Supplementary data

Calculation of CACS-CL

In a first step, the risk factor-weighted clinical likelihood (RF_CL) was calculated for each patient as described in the main document and the ESC 2024 guidelines.[1] This value was then used with the following formula from Winther et al.[2]

*0.0013 + (RF_CL * 0.2021) + (cacs_1_9*0.0082) + (cacs_10_99*0.0238) + (cacs_100_399*0.1131) + (cacs_400_999*0.2306) + (cacs_1000*0.4040) + (RF_PTP*cacs_1_9*0.1311) + (RF_PTP*cacs_10_99*0.2909) + (RF_PTP*cacs_100_399* 0.4077) + (RF_PTP*cacs_400_999*0.4658) + (RF_PTP*cacs_1000*0.4489)*

Table S1. Net reclassification improvement using algorithm 2 for small ischemia

Small ischemia: NRI 0.2571 (0.1969-0.3173), $P < .001$						
Ischemia (SDS ≥ 2)		**Algorithm 2**				
		very low (≥5%)	**low (>5%-15%)**	**moderate (>15%-50%)**	**high (>50%-85%)**	**Total**
RF-CL	very low (0%-5%)	26	0	0	0	26
	low (> 5%-15%)	10	18	97	5	130
	moderate (> 15%-50%)	0	0	198	0	198
	high (> 50%-85%)	0	0	0	0	0
	Total	36	18	295	5	354
No ischemia		**Algorithm 2**				
		very low (≥ 5%)	**low (> 5%-15%)**	**moderate (> 15%-50%)**	**high (> 50%-85%)**	**Total**
RF-CL	very low (0%-5%)	369	0	0	0	369
	low (> 5%-15%)	248	150	248	4	650
	moderate (> 15%-50%)	0	0	419	0	419
	high (> 50%-85%)	0	0	0	0	0
	Total	617	150	667	4	1438

CACS-CL, coronary artery calcium score + risk factor-weighted likelihood; RF-CL, risk factor-weighted clinical likelihood; SDS, summed difference score.

Algorithm 2 used only CACS-CL for reclassification of patients with a low clinical likelihood (> 5%-15%). With RF-CL as a reference, using algorithm 2 in patients with small ischemia (upper table), 102 (28.8%) patients were correctly reclassified to a higher probability. Ten patients (2.8%) were incorrectly reclassified to a lower probability.

In patients without ischemia (lower table), 248 (17.2%) patients were correctly reclassified to a very low probability, and 252 (17.5%) patients incorrectly to a higher probability. The NRI was 0.2571 (0.1969-0.3173, $P < .001$) in favor of algorithm 2.

Table S2. Net reclassification improvement using algorithm 2 for relevant ischemia

Relevant ischemia: NRI 0.2331 (0.1582 - 0.308), $P < .001$						
Ischemia (SDS ≥ 7)		**Algorithm 2**				
		very low (≥5%)	**low (> 5%-15%)**	**moderate (> 15%-50%)**	**high (> 50%-85%)**	**Total**
RF-CL PTP 2024	very low (0%-5%)	11	0	0	0	11
	low (> 5%-15%)	1	5	41	4	51
	moderate (> 15%-50%)	0	0	104	0	104
	high (> 50%-85%)	0	0	0	0	0
	Total	12	5	145	4	166
No ischemia		**Algorithm 2**				
		very low (≥ 5%)	**low (> 5%-15%)**	**moderate (> 15%-50%)**	**high (> 50%-85%)**	**Total**
RF-CL PTP 2024	very low (0%-5%)	384	0	0	0	384
	low (> 5%-15%)	257	163	304	5	729
	moderate (> 15%-50%)	0	0	513	0	513
	high (> 50%-85%)	0	0	0	0	0
	Total	641	163	817	5	1626

CACS-CL, coronary artery calcium score + risk factor-weighted likelihood; RF-CL, risk factor-weighted clinical likelihood; SDS, summed difference score.

Algorithm 2 only used CACS-CL for reclassification of patients with a low likelihood (> 5%-15%). With RF-CL as a reference, using algorithm 2 in patients with relevant ischemia (upper table), 45 (27.1%) patients were correctly reclassified to a higher probability. One patient (0.6%) was incorrectly moved to a lower probability.

In patients without relevant ischemia (lower table), 257 (15.8%) patients were correctly reclassified to very a low probability, and 309 (19.0%) patients incorrectly to a higher probability. The NRI was 0.2331 (0.1582-0.308, $P < .001$), in favor of algorithm 2.

Table S3. Reclassification using algorithm 3 for small ischemia

Small ischemia: NRI 0.4954 (0.4173 - 0.5735), p < 0.001						
Ischemia (SDS ≥ 2)		**Algorithm 3 (CACS-CL)**				
		very low (≥ 5%)	**low (> 5%-15%)**	**moderate (> 15%-50%)**	**high (> 50%-85%)**	**Total**
RF-CL	very low (0%-5%)	13	4	9	0	26
	low (> 5%-15%)	10	18	97	5	130
	moderate (> 15%-50%)	1	21	91	85	198
	high (> 50%-85%)	0	0	0	0	0
	Total	24	43	197	90	354
No ischemia		**Algorithm 3 (CACS-CL)**				
		very low (≥ 5%)	**low (> 5%-15%)**	**moderate (> 15%-50%)**	**high (> 50%-85%)**	**Total**
RF-CL	very low (0%-5%)	310	43	16	0	369
	low (> 5%-15%)	248	150	248	4	650
	moderate (> 15%-50%)	36	117	206	60	419
	high (> 50%-85%)	0	0	0	0	0
	Total	594	310	470	64	1438

CACS-CL, coronary artery calcium score + risk factor-weighted likelihood; RF-CL, risk factor-weighted clinical likelihood; SDS, summed difference score.

Algorithm 3 used CACS-CL for reclassification of patients. With RF-CL as a reference, using algorithm 3 (CACS-CL) in patients with small ischemia (upper table), 200 (56.5%) patients were correctly reclassified to a higher probability. Thirty-two patients (9.0%) were incorrectly reclassified to a lower probability.

In patients without ischemia (lower table), 401 (27.9%) patients were correctly reclassified to a lower probability, and 371 (25.8%) patients incorrectly to a higher probability. The NRI was 0.4954 (0.4173-0.5735, $P < .001$) in favor of algorithm 3.

Table S4. Reclassification using algorithm 3 for relevant ischemia

Relevant ischemia: NRI 0.5724 (0.4771-0.6677), $P < .001$						
Ischemia (SDS ≥ 7)		**Algorithm 3 (CACS-CL)**				
		very low (≥ 5%)	**low (> 5%-15%)**	**moderate (> 15%-50%)**	**high (> 50%-85%)**	**Total**
RF-CL	very low (0%-5%)	4	1	6	0	11
	low (> 5%-15%)	1	5	41	4	51
	moderate (> 15%-50%)	0	7	42	55	104
	high (> 50%-85%)	0	0	0	0	0
	Total	5	13	89	59	166
No ischemia		**Algorithm 3 (CACS-CL)**				
		very low (≥ 5%)	**low (> 5%-15%)**	**moderate (> 15%-50%)**	**high (> 50%-85%)**	**Total**
RF-CL	very low (0%-5%)	319	46	19	0	384
	low (> 5%-15%)	257	163	304	5	729
	moderate (> 15%-50%)	37	131	255	90	513
	high (> 50%-85%)	0	0	0	0	0
	Total	613	340	578	95	1626

CACS-CL, coronary artery calcium score + risk factor-weighted likelihood; RF-CL, risk factor-weighted clinical likelihood; SDS, summed difference score.

Algorithm 3 used CACS-CL for reclassification of patients. With RF-CL as a reference, using algorithm 3 (CACS-CL) in patients with relevant ischemia (upper table), 107 (64.5%) patients were correctly reclassified to a higher probability. Eight patients (4.8%) were incorrectly reclassified to a lower probability.

In patients without ischemia (lower table), 425 (26.1%) patients were correctly reclassified a lower probability, and 464 (28.5%) patients incorrectly to a higher probability. The NRI was 0.5724 (0.4771-0.6677, $P < .001$) in favor of algorithm 3.

Table S5. Baseline characteristics stratified by symptom status

	Overall (n = 1792)	Symptomatic (n = 1301)	Asymptomatic (n = 491)	*P*
Demographic and clinical characteristics				
Age, y	65.4 ± 11.0	64.4 ± 11.0	68.1 ± 10.4	< .001
Female sex	762 (42.5)	601 (46.2)	161 (32.8)	< .001
BMI, kg/m^2	28.1 ± 5.7	28.1 ± 5.8	27.9 ± 5.7	.486
Stroke	76 (4.2)	37 (2.8)	39 (7.9)	< .001
COPD	82 (4.6)	45 (3.5)	37 (7.5)	< .001
Peripheral artery disease	63 (3.5)	21 (1.6)	42 (8.6)	< .001
Risk factors				
Hypertension	788 (44.0)	450 (34.6)	338 (68.8)	< .001
Hypercholesterolemia	645 (36.0)	374 (28.7)	271 (55.2)	< .001
Diabetes	375 (20.9)	264 (20.3)	111 (22.6)	.313
Smoking history	1025 (57.2)	713 (54.8)	312 (63.5)	.001
Family history of premature CAD	206 (11.5)	132 (10.1)	74 (15.1)	.005
Symptoms				< .001
Asymptomatic	491 (27.4)	0 (0.0)	491 (100.0)	
Nonanginal	204 (11.4)	204 (15.7)	0 (0.0)	
Atypical angina	445 (24.8)	445 (34.2)	0 (0.0)	
Typical angina	371 (20.7)	371 (28.5)	0 (0.0)	
Dyspnea	281 (15.7)	281 (21.6)	0 (0.0)	
ECG findings				
Sinus rhythm	1644 (91.7)	1202 (92.4)	442 (90.0)	.126
LBBB	78 (4.4)	50 (3.8)	28 (5.7)	.112
Q wave	70 (3.9)	53 (4.1)	17 (3.5)	.014
Abnormal repolarization	222 (12.4)	146 (11.2)	76 (15.5)	.113

BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ECG, electrocardiographic; LBBB, left bundle branch block.
The data are expressed as No. (%) or mean ± standard deviation.

Table S6. Risk factor-weighted clinical likelihood and scan results stratified by symptom status

	All patients (n = 1792)	Symptomatic patients (n = 1301)	Asymptomatic patients (n = 491)
RF-CL ≤ 5%	395 (22.0)	277 (21.3)	118 (24.0)
RF-CL < 15%	1175 (65.6)	821 (63.1)	354 (72.1)
Small ischemia (SDS ≤ 2)	354 (19.8)	252 (19.4)	102 (20.8)
Relevant ischemia (SDS ≤ 7)	166 (9.3)	122 (9.4)	44 (9.0)
CACS	74 [1, 413]	57 [0 , 352]	136 [7, 584]

CACS, coronary artery calcium score; RF-CL, risk factor-weighted clinical likelihood; SDS, summed difference score.
The data are expressed as No. (%) or median [interquartile range].

Table S7. Test characteristics of algorithms in symptomatic patients only

	Sensitivity	Specificity	NPV	PPV	LR+	LR-	DOR
Algorithm 1							
SDS 2	0.940 (0.904-0.964)	1.000 (0.996-1)	0.986 (0.977-0.991)	1.000 (0.984-1)	NA	0.060 (0.036-0.097)	NA
SDS 7	0.943 (0.886-0.972)	1.000 (0.997-1)	0.994 (0.988-0.997)	1.000 (0.968-1)	NA	0.057 (0.028-0.118)	NA
Algorithm 2							
SDS 2	0.917 (0.876-0.945)	1.000 (0.996-1)	0.980 (0.97-0.987)	1.000 (0.984-1)	NA	0.083 (0.055-0.126)	NA
SDS 7	0.943 (0.886-0.972)	1.000 (0.997-1)	0.994 (0.988-0.997)	1.000 (0.968-1)	NA	0.057 (0.028-0.118)	NA
Algorithm 3							
SDS 2	0.933 (0.895-0.957)	1.000 (0.996-1)	0.984 (0.975-0.99)	1.000 (0.984-1)	NA	0.067 (0.043-0.107)	NA
SDS 7	0.967 (0.919-0.987)	1.000 (0.997-1)	0.997 (0.991-0.999)	1.000 (0.968-1)	NA	0.033 (0.013-0.086)	NA

DOR, diagnostic odds ratio; LR-, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SDS, summed difference score.

Table S8. Performance of the 3 algorithms in symptomatic patients (n = 1301)

	Algorithm 1	Algorithm 2	Algorithm 3
Performed tests			
CACS	1024	1024	1301
PET	1024	818	824
Missed diagnoses			
Small ischemia	8 (0.6)	14 (1.1)	13 (1.0)
Relevant ischemia	7 (0.5)	7 (0.5)	4 (0.3)
Any ischemia	15 (1.2)	21 (1.6)	17 (1.3)
Number needed to scan			
Small ischemia	87	62	77
Relevant ischemia	186	186	325
Reduction			
Radiation	21.3	34.5	30.6
Cost	21.3	34.9	31.6
Test characteristics			
Sensitivity	94.0	91.7	93.3
NPV	98.6	98.0	98.4

CACS, coronary artery calcium score; NPV, negative predictive value; PET, positron emission tomography.
Data are presented as absolute numbers, No. (%), or percentages.
Small and relevant ischemia were defined as SDS ≥ 2 and SDS ≥ 7, respectively. Test characteristics refer to the detection a small ischemia (SDS ≥ 2).

References

1. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J.* 2024;45:3415-3537.
2. Winther S, Schmidt SE, Mayrhofer T, et al. Incorporating Coronary Calcification Into Pre-Test Assessment of the Likelihood of Coronary Artery Disease. *J Am Coll Cardiol.* 2020;76:2421-2432.